

REMARKS

Claims 1-17 and 21-26 are rejected. Applicants thank the Examiner for granting a telephonic interview on February 7, 2006 to discuss the Office Action. No agreement was reached. Applicants also thank the Examiner for granting a telephonic interview with the undersigned on May 3, 2006 at 12:30 pm (EST). The telephonic interview will also be attended by Professor Hennink, who is one of the inventors, and by Harrie Marsman, who is a representative of the client and an agent of the undersigned.

Rejections under 35 U.S.C. § 102(b)

Claims 1-5, 7-10 and 13 remain rejected under 35 U.S.C. § 102(b), as allegedly being anticipated by Okihara *et al.* The Office alleged that the oligomers are water-soluble and the claims do not exclude organic solvent. Applicants respectfully disagree.

As indicated in Professor Hennink's declaration (Hennink Decl. II, attached as Exhibit A), hydrogels generally contain from about 20 to more than 99 weight % water, and in the absence of water, a stereocomplex described in Okihara cannot form a hydrogel. (Hennink Decl. II at paragraphs 3-4). Unlike Okihara, the present invention covers a hydrogel composition comprising a mixture of two polymers in an aqueous system. Whether or not the claims include an organic solvent is irrelevant to the patentability of the claims under Okihara, because Okihara fails to teach aqueous systems at all. (Hennink Dec. II at paragraphs 3-5).

To anticipate a claim, the reference must teach each and every element of the claim. Even if the Office alleges that Okihara teaches water-soluble polymers, which as previously described in Professor Hennink's declaration is not the case, Okihara nonetheless fails to anticipate because it fails to teach aqueous systems or hydrogel compositions which contain water. Because Okihara fails to teach all the elements of the invention, the claims are not anticipated. Applicants therefore, respectfully request that this rejection be withdrawn.

Claims 1-10, 14 and 21-26 remain rejected under 35 U.S.C. § 102(b), as allegedly being anticipated by Hennink *et al.* (WO 98/00170). The Office alleged that no specific chirality is recited in the claims and the claims do not exclude or include covalent or noncovalent interaction. Applicants disagree because the claims specifically require noncovalent interaction, and require two chiral groups of opposite chirality (*e.g.*, enantiomeric groups).

As indicated in the Hennink Decl. II, the only reference to an isomeric form of lactide in WO 98/00170 is in Example 3, which describes the synthesis of dextran-(L-lactide)-HEMA. Other examples teach the use of (poly)glycolic acid as a spacer between polymerizable methacrylate groups and dextran. (Hennink Decl. II at paragraphs 7-8). Because the cited art fails to teach two polymeric groups each having complementary chiral groups that interact noncovalently with each other, WO 98/00170 does not anticipate the claims. Applicants therefore, respectfully request that this rejection be withdrawn.

Rejections under 35 U.S.C. § 103

Claim 11 remains rejected under 35 U.S.C. § 103(a), as allegedly being unpatentable over Hennink *et al.* (WO 98/00170). Applicants respectfully disagree.. The WO 98/00170 publication neither teaches nor suggests polymers substituted with complementary chiral groups that interact noncovalently with each other. Thus, WO 98/00170 does not anticipate or render obvious claim 1. Because claim 11 contains all the limitations of claim 1, claim 11 is unobvious under WO 98/00170.

Claim 12, which depends on claim 1, was rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Okihara. Applicants again respectfully disagree. As previously indicated, Okihara neither teaches nor suggests polymers in an aqueous system at all, and Okihara fails to teach hydrogel compositions. Thus, Okihara does not anticipate or render obvious claim 1. Because claim 12 contains all the limitations of claim 1, claim 12 is unobvious under Okihara.

Claims 15-17 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over De Jong *et al.* (Macromolecules (1998) 31:6397-402) in view of Brannon-Peppas (Int. J. Pharm. (1995) 116:1-9). Applicants respectfully disagree.

Contrary to the Examiner's assertions, the stereocomplexes in De Jong *et al.* (Macromolecules 31:6397-6402 (1998)) are not hydrogels. As previously indicated, it is impossible to form a hydrogel in the absence of water. Unlike the invention as claimed, the De Jong reference teaches the preparation of stereocomplexes in the absence of water. Rather, as the Office noted, polydisperse lactic acid oligomers were prepared using 2-(2-methoxyethoxy)ethanol as initiator and stannous octoate as catalyst at 130 °C until the lactide was molten. (See De Jong *et al.*, at page 6399 and 6401).

The failure to teach the preparation of a hydrogel from mixtures in an aqueous system is not remedied by the combination with Brannon-Peppas (Int. J. Pharm. 116:1-9 (1995)), which merely describes the use of biodegradable polymers in controlled drug delivery. Thus, even if De Jong and Brannon-Peppas were combined, the combination still fails to teach the process as claimed. Accordingly, claims 15-17 are nonobvious under De Jong, in view of Brannon-Peppas, and Applicants respectfully request that this rejection be withdrawn.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 313632001000. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: April 25, 2006

Respectfully submitted,

By Emily C. Tongco
Emily C. Tongco

Registration No.: 46,473
MORRISON & FOERSTER LLP
12531 High Bluff Drive
Suite 100
San Diego, California 92130-2040
(858) 314-5413



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(Judy Bridgwater)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Wilhelmus Evergardu HENNINK et al.

Application No.: 09/913,967

Art Unit: 1615

Filed: (Int.) February 21, 2000

Examiner: B. Fubara

For: STEREOCOMPLEX HYDROGELS

DECLARATION OF WILHELMUS EVERHARDUS HENNINK
UNDER 37 C.F.R. § 1.132

MS RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, Wilhelmus Everhardus Hennink of Zuidplasmaan 120 NL-2743 CZ Waddinxveen, the Netherlands, declare as follows:

1. I am a professor at the University of Utrecht, and an expert in the field of hydrogels, as evidenced by my *curriculum vitae* submitted with my previous declaration dated January 20, 2005, which is incorporated herein by reference. I am an inventor in the present application and am also a co-inventor in WO 98/00170.
2. I have reviewed the Final Office Action mailed January 27, 2006. This declaration is submitted in response to the Final Office Action to distinguish the present invention from the prior art references.

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3. A hydrogel is a polymer swollen in or with water. (See e.g., McGraw-Hill Dictionary of Scientific and Technical Terms, attached as Exhibit 1, a hydrogel is "[t]he formation of a colloid in which the disperse phase (colloid) has combined with the continuous phase (water) to produce a jellylike product.") As known in the art, hydrogels generally contain from about 20 to more than 99 weight % water. (See e.g., WO 98/00170 at page 5). The claimed compositions also explicitly require a mixture of polymers in an aqueous system, thereby containing water.

4. The Okihara reference (J. Macromol. Sci. Phys. B30 (1 & 2) 119-140 (1990)) describes non-aqueous crystalline structures of a polylactide stereocomplex. In Okihara, poly(D-lactic acid) and poly(L-lactic acid) are heated to form a polymer melt after evaporation of an organic solvent. (See, J. Macromol. Sci. Phys. B30 (1 & 2) at pages 120 and 121). In the absence of water, the stereocomplex described in Okihara cannot form a hydrogel.

5. In maintaining the anticipation rejection under Okihara, the Office indicated that my previous declaration "stating that hydrogel cannot form in the absence of water is not commensurate with the claims because the claims have not excluded organic solvent. The oligomers of the claims and the prior art are water-soluble." (Final Office Action mailed January 27, 2006, at page 2). Whether or not the claims include an organic solvent is irrelevant to the patentability of the claims in view of Okihara, because Okihara fails to teach aqueous systems at all and the invention as claimed contains an aqueous system.

6. The WO 98/00170 publication describes covalently crosslinked hydrogels prepared by free radical polymerization of a crosslinkable group. As the Office correctly indicated, (poly)glycolic acid and/or (poly)lactic acid spacers are introduced between polymerizable methacrylate groups and dextran, and the hydrogel is prepared by a radical polymerization in the presence of an initiator. (Final Office Action, page 3). Unlike the hydrogels as claimed, the substituted dextran polymers in WO 98/00170 do not contain chiral monomers that are complementary to each other.

7. Poly(glycolic acid) is formed from glycolic acid ($\text{OH-CH}_2\text{-CO}_2\text{H}$), which lacks a chiral carbon and therefore cannot form enantiomers (*i.e.*, non-superimposable mirror-image forms of chiral molecules). A racemic mixture requires equal amounts of two enantiomers; since glycolic acid is not chiral, there can be no enantiomers and poly(glycolic acid) is not a racemic mixture. The only reference to an isomeric form of the lactide in WO 98/00170 is found in Example 3, which describes the synthesis of dextran-(L-lactide)-HEMA, and the preparation of the hydrogel by free radical polymerization as described in Example 5. Thus, WO 98/00170 fails to teach two types of polymers, each having a chiral substituent that is complementary to the other.

8. In maintaining the rejections under the WO 98/00170 publication, the Office indicated that "a racemic molecule has equal components of each component of opposite chirality. . . [I]t is noted that no specific chirality is recited and the composition claims do not exclude of [sic] exclude covalent or non-covalent interaction." (Final Office Action mailed January 27, 2006, at page 3). Whether or not the claims exclude covalent interactions is irrelevant to the patentability of the claims in view of WO 98/00170, because the cited art fails to teach two polymeric groups each having complementary chiral groups that interact noncovalently with each other. Furthermore, the physical interaction between the grafts formed from monomers of opposite chirality is different from the physical interaction that occurs when the grafts were formed from a racemic mixture of the same monomers. (See, WO 00/48576 at page 7, lines 22-20.)

9. The Office correctly indicates that the claims do not exclude non-covalent interactions between the polymers. Rather, the claims require that the oligomer or co-oligomer groups in polymer mixture A are complementary in chirality and interact noncovalently with the oligomer or co-oligomer groups in polymer mixture B. Because WO 98/00170 fails to teach two polymeric groups each having complementary chiral groups, the polymers in WO 98/00170 are incapable of interacting noncovalently with each other.

10. For the Examiner's reference, a schematic representation of the covalently crosslinked hydrogels formed by free radical polymerization as described in WO 98/00170 is shown

in Exhibit 2. The covalently crosslinked hydrogels are clearly distinguishable from the non-covalently crosslinked hydrogels of the invention as claimed, shown in Exhibit 3.

11. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: April 19th 2006



Wilhelmus Everhardus Hennink

McGraw-Hill Dictionary of Scientific and Technical Terms

Fifth Edition

Sybil P. Parker
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of hydrogen and carbon monoxide in the presence of a cobalt catalyst. { 'hī-drā-fōrmə'lā-shən }

hydrofuge [ZOO] Of a structure, shedding water, as the hair on certain animals. { 'hī-drā-fyūj }

hydrogarnet [MINERAL] One of a group of minerals having the general formula $A_3B_2(SiO_4)_3-x(OH)_x$; isomorphous with certain garnets. { 'hī-drō-gār-nət }

hydrogasification [CHEM ENG] A technique to manufacture synthetic pipeline gas from coal; pulverized coal is reacted with hot, raw, hydrogen-rich gas containing a substantial amount of steam at 1000 pounds per square inch gage (6.9×10^6 pascals, gage) to form methane. { 'hī-drā-gas-ə-fā-kā-shən }

hydrogel [CHEM] The formation of a colloid in which the disperse phase (colloid) has combined with the continuous phase (water) to produce a viscous jellylike product; for example, coagulated silicic acid. { 'hī-drā-jel }

hydrogen [CHEM] The first chemical element, symbol H, in the periodic table, atomic number 1, atomic weight 1.00797; under ordinary conditions it is a colorless, odorless, tasteless gas composed of diatomic molecules, H_2 ; used in manufacture of ammonia and methanol, for hydrofining, for desulfurization of petroleum products, and to reduce metallic oxide ores. { 'hī-drā-jən }

hydrogenase [BIOCHEM] Enzyme that catalyzes the oxidation of hydrogen. { 'hī-drāj-ə-nās }

hydrogenated oil [ORG CHEM] Unsaturated liquid vegetable oil that has had hydrogen catalytically added so as to convert the oil to a hydrogen-saturated solid. { 'hī-drā-jə-nād-əd 'ōil }

hydrogenation [CHEM ENG] Saturation of diolefin impurities in gasolines to form a stable product. [ORG CHEM] Catalytic reaction of hydrogen with other compounds, usually unsaturated; for example, unsaturated cottonseed oil is hydrogenated to form solid fats. { 'hī-drāj-ə-nā-shən }

hydrogen bacteria [MICROBIO] Bacteria capable of obtaining energy from the oxidation of molecular hydrogen. { 'hī-drā-jən bak'tīrē-ə }

hydrogen blistering [MET] Cracks or blisters caused when atomic hydrogen penetrates steel via submicroscopic discontinuities or voids and becomes molecular hydrogen and develops internal pressures. { 'hī-drā-jən 'blīst-ər-īŋ }

hydrogen bomb [ORD] A device in which heavy hydrogen nuclei, under intense heat and pressure, undergo an uncontrolled, self-sustaining fusion reaction to produce an explosion. Also known as H bomb. { 'hī-drā-jən 'bām }

hydrogen bond [PHYS CHEM] A type of bond formed when a hydrogen atom bonded to atom A in one molecule makes an additional bond to atom B either in the same or another molecule; the strongest hydrogen bonds are formed when A and B are highly electronegative atoms, such as fluorine, oxygen, or nitrogen. { 'hī-drā-jən 'bānd }

hydrogen brazing [MET] Brazing in an atmosphere rich in hydrogen. { 'hī-drā-jən 'brāz-īŋ }

hydrogen bromide [INORG CHEM] HBr A hazardous, toxic gas used as a chemical intermediate and as an alkylation catalyst; forms hydrobromic acid in aqueous solution. { 'hī-drā-jən 'brō-mīd }

hydrogen-bubble method [FL MECH] A method of flow visualization in which hydrogen bubbles are generated by electrolysis of water using wire electrodes, and are made to form either time lines (by applying a pulsating voltage to a bare cathode) or streamlines (by applying a continuous voltage to a kink in an insulated cathode). { 'hī-drā-jən 'bāb-əl 'meth-əd }

hydrogen burning [ASTROPHYS] Thermonuclear reactions occurring in the cores of main-sequence stars, in which nuclei of hydrogen fuse to form helium nuclei. { 'hī-drā-jən 'bārn-īŋ }

hydrogen chloride [INORG CHEM] HCl A fuming, highly toxic, colorless gas soluble in water, alcohol, and ether; used in the production of vinyl chloride and alkyl chloride, and in polymerization, isomerization, and other reactions. { 'hī-drā-jən 'klōr-īd }

hydrogen cyanide See hydrocyanic acid. { 'hī-drā-jən 'sī-ə-nīd }

hydrogen cyanide laser [OPTICS] A gas laser using hydrogen cyanide, which emits infrared radiation at wavelengths of 311 and 337 micrometers. { 'hī-drā-jən 'sī-ə-nīd 'lā-zər }

hydrogen cycle [CHEM] The complete process of a cation-exchange operation in which the adsorbent is used in the hydrogen or free acid form. { 'hī-drā-jən 'sī-kəl }

hydrogen damage [MET] Corrosion, common in boilers, caused by diffusion of hydrogen through steel reacting with carbon to form methane, which builds up local stresses at the interfaces between grains, forming voids that ultimately produce failure. { 'hī-drā-jən 'dam-ij }

hydrogen discharge lamp [ELECTR] A discharge lamp containing hydrogen and used as a source of ultraviolet radiation. { 'hī-drā-jən 'dis-čärj 'lamp }

hydrogen disulfide See hydrogen sulfide. { 'hī-drā-jən dī'səl-fīd }

hydrogen electrode [PHYS CHEM] A noble metal (such as platinum) of large surface area covered with hydrogen gas in a solution of hydrogen ion saturated with hydrogen gas; metal is used in a foil form and is welded to a wire sealed in the bottom of a hollow glass tube, which is partially filled with mercury; used as a standard electrode with a potential of zero to measure hydrogen ion activity. { 'hī-drā-jən i'lek-trōd }

hydrogen embrittlement See acid brittleness. { 'hī-drā-jən em'brīd-əl-mənt }

hydrogen equivalent [CHEM] The number of replaceable hydrogen atoms or hydroxyl groups in a molecule of an acid or a base. { 'hī-drā-jən i'kwiv-ə-lənt }

hydrogen fluoride [INORG CHEM] HF The hydride of fluorine; anhydrous HF is a mobile, colorless, liquid that fumes in air, melts at -83°C , boils at 19.8°C ; used to make fluorine-containing refrigerants (such as Freon) and organic fluorocarbon compounds, as a catalyst in alkylate gasoline manufacture, as a fluorinating agent, and in preparation of hydrofluoric acid. { 'hī-drā-jən 'flūr-īd }

hydrogenic ion [ATOM PHYS] An atom from which all but one of the electrons have been removed. { 'hī-drā-jen-ik 'ī-ān }

hydrogenic rock See aqueous rock. { 'hī-drā-jen-ik 'rāk }

hydrogen iodide [INORG CHEM] HI A water-soluble, colorless gas that may be used in organic synthesis and as a reagent. Also known as hydriodic acid gas. { 'hī-drā-jən 'ī-ə-dīd }

hydrogen ion See hydronium ion. { 'hī-drā-jən 'ī-ān }

hydrogen ion concentration [CHEM] The normality of a solution with respect to hydrogen ions, H^+ ; it is related to acidity measurements in most cases by $\text{pH} = \log 1/2 [1/(H^+)]$, where (H^+) is the hydrogen ion concentration in gram equivalents per liter of solution. { 'hī-drā-jən 'ī-ān 'kāns-ən-trā-shən }

hydrogen ion exponent [CHEM] A way of expressing pH; namely, $\text{pH} = -\log c_H$, where c_H = hydrogen ion concentration. { 'hī-drā-jən 'ī-ān ik'spō-nənt }

hydrogen laser [OPTICS] A molecular gas laser in which hydrogen is used to generate coherent wavelengths near 0.6 micrometer in the vacuum ultraviolet region. { 'hī-drā-jən 'lā-zər }

hydrogen line [SPECT] A spectral line emitted by neutral hydrogen having a frequency of 1420 megahertz and a wavelength of 21 centimeters; radiation from this line is used in radio astronomy to study the amount and velocity of hydrogen in the Galaxy. { 'hī-drā-jən 'līn }

hydrogen loss [MET] Loss of weight by a compact or a metal powder when heated in a hydrogen atmosphere; used as a measure of oxygen content of the sample. { 'hī-drā-jən 'lōs }

hydrogen maser [PHYS] A maser in which hydrogen gas is the basis for providing an output signal with a high degree of stability and spectral purity. { 'hī-drā-jən 'mā-zər }

hydrogenolysis [CHEM] A reaction in which hydrogen gas causes a chemical change that is similar to the role of water in hydrolysis. { 'hī-drā-jə-nāl-ə-səs }

hydrogenous [CHEM] Of, pertaining to, or containing hydrogen. { 'hī-drāj-ə-nəs }

hydrogen overvoltage [MET] An overvoltage occurring at an electrode as a result of the liberation of hydrogen gas. { 'hī-drā-jən 'ō-vər-vōlt-ij }

hydrogen oxide See water. { 'hī-drā-jən 'āk-sīd }

hydrogen peroxide [INORG CHEM] H_2O_2 Unstable, colorless, heavy liquid boiling at 158°C ; soluble in water and alcohol; used as a bleach, chemical intermediate, rocket fuel, and antiseptic. Also known as peroxide. { 'hī-drā-jən pə'rāk-sīd }

hydrogen phosphide See phosphine. { 'hī-drā-jən 'fās-fīd }

hydrogen-reduced powder [MET] Metal powder produced by hydrogen-reduction of a metal, metallic compound, or surface-contaminated metal particles. { 'hī-drā-jən nī'düst 'paūd-ər }

hydrogen selenide [INORG CHEM] H_2Se A toxic, colorless gas, soluble in water, carbon disulfide, and phosgene; used to

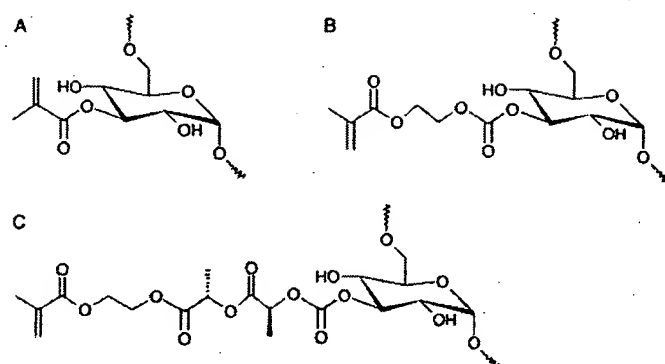


Fig. 2. Structures of (A) dex-MA, (B) dex-HEMA and (C) dex-(lactate)₂-HEMA.

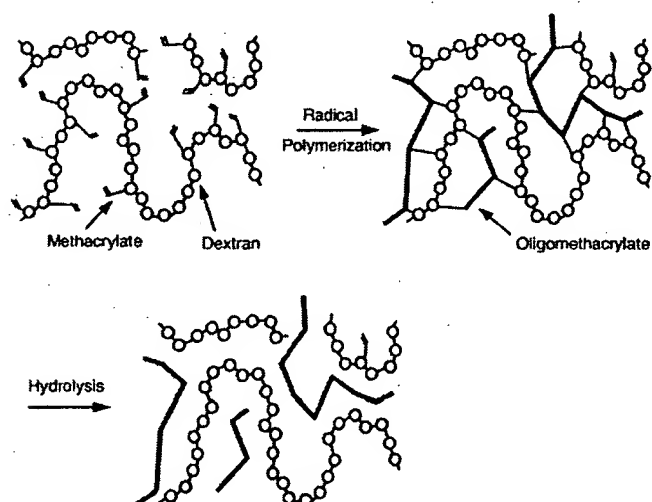
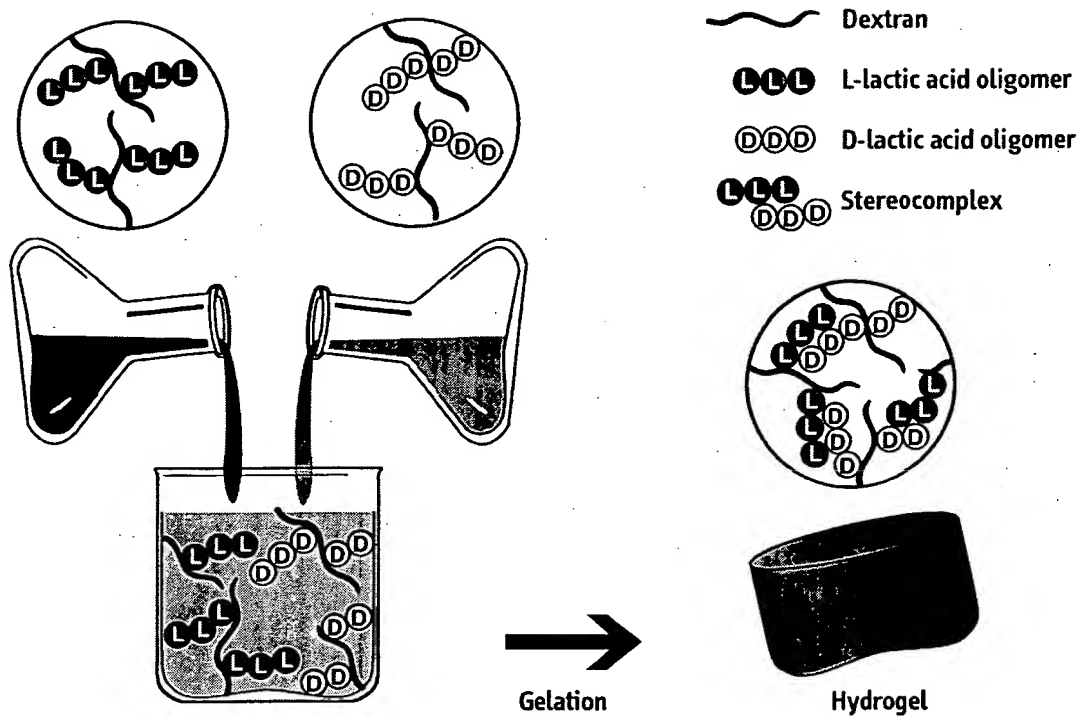


Fig. 3. Schematic representation of the formation and degradation (for dex-HEMA and dex-(lactate)₂-HEMA) of dextran hydrogels. Gels are formed by radical polymerization of the methacrylate groups using KPS and TEMED as initiator system. Degradation occurs by hydrolysis of the carbonate and lactate ester for dex-HEMA and dex-(lactate)₂-HEMA, respectively.



The concept of the stereocomplex hydrogel system. The hydrogel is obtained after mixing aqueous solutions of dex-(L)-lactate (L-lactic acid oligomer grafted to dextran) and dex-(D)-lactate.

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